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(54) **COMPOUNDS, FORMULATIONS, AND METHODS FOR TREATING OR PREVENTING ROSACEA**

VERBINDUNGEN, FORMULIERUNGEN UND VERFAHREN ZUR BEHANDLUNG ODER PRÄVENTION VON ROSACEA

COMPOSES, PREPARATIONS ET METHODES DE TRAITEMENT OU DE PREVENTION DE LA ROSACEE

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Description

Cross-Reference To Related Application

[0001] This application claims priority from U.S. Patent Application Serial No. 10/853,585, filed on May 25, 2004 and U.S. Patent Application Serial No. 60/473,611, filed on May 27, 2003.

Field Of The Invention

[0002] The present invention is directed to compositions for use in methods for the topical treatment of rosacea-induced redness. The compounds taught by the present invention are useful for treating rosacea-induced redness.

Background Of The Invention

[0003] Many people are affected by inflammatory skin disorders that result in unsightly and painful rashes, acne, persistent red veins, and acne-like skin eruptions, such as macules, nodules, and pustules that may ooze or crust. Inflammatory skin disorders often result in intense psychosocial distress. Rosacea is a common inflammatory skin disorder affecting over 10 million people in the United States. Rosacea generally involves the cheeks, nose, chin, and forehead and the typical age of onset is 30 to 60 years. See e.g., Zuber T.J., Rosacea: Beyond First Blush 32 HOSP. PRACT. 188-189 (1997); THE MERCK MANUAL 813-814 (Keryn A.G. Lane et al. eds. 17th ed. 2001). Many people with early-stage rosacea incorrectly assume that they suffer from adult acne, sun or windburn, or the normal effects of aging.

[0004] Rosacea develops gradually starting as frequent blushing and frequent irritation of the facial skin. More advanced rosacea is characterized by a vascular stage where patients display increasingly severe erythema (abnormal redness of the skin) and telangiectasia (visible red lines due to abnormal dilatation of capillary vessels and arterioles). Pimple-like eruptions, which may be solid (called papules or nodules) or puss filled (known as pustules) may develop. Such eruptions often look like acne, but whiteheads or blackheads (common symptoms of acne) are not normally present. Later-stage rosacea is characterized by rhinophyma (enlargement of the nose). If left untreated, rosacea can progress to irreversible disfigurement. Rosacea symptoms are often aggravated by sun exposure, changes or extremes in temperature, wind, and consumption of certain foods, such as spicy foods, caffeine, and alcohol.

[0005] The exact pathogenesis of rosacea is unknown, but the pathologic process is well described. For example, erythema associated with rosacea is caused by dilation of the superficial vasculature of the face. Zuber T.J., Rosacea: Beyond First Blush 32 HOSP. PRAT. 188-189 (1997).

[0006] There is no known cure for rosacea. Current treatments, which are directed to control of redness, inflammation, and skin eruptions, are of limited effectiveness in many patients and, generally, can be used only for a limited duration. Standard treatments include avoidance of triggers such as sun exposure, wind exposure, alcohol consumption, spicy foods, and irritating facial cleansers, lotions, and cosmetics. Antibiotics are the traditional first line of therapy. Long-term treatment (5 to 8 weeks or more) with oral antibiotics such as tetracycline, minocycline, doxycycline or clarithromycin may control skin eruptions. Alternative oral treatments include vitamin A medications, such as isoretinoin and antifungal medications. Unfortunately, such oral medications often cause side effects and many people have limited tolerance. Topical treatments, such at topically applied antibiotics and antifungals (such as metronidazole) or steroids, are available but also have limited effectiveness and cannot treat all symptoms. For example, isoretinoin has serious teratogenic side-effects and female patients of child bearing age must use effective birth control or avoid the therapy. Topical treatments include topically applied metronidazole, topically applied steroids, topically applied azelaic acid, topically applied rentinoic acid or retinaldehyde, and topical vitamin C preparations are available but have limited effectiveness and cannot treat all symptoms. Surgery, such as the laser elimination of blood vessels, is typically a last resort, but may be prescribed if other treatments are ineffective. In patients with nose hyperplasia, surgical reduction may improve the patient's cosmetic appearance, but does not treat the disease itself. Mixed light pulse (photoderm) therapy has proved somewhat effective for certain rosacea symptoms in some patients. Thus, there remains a need for topical formulations for treatment of rosacea and its symptoms.

[0007] Agonists of the α_2 adrenoceptors have been used therapeutically for a number of conditions including hypertension, congestive heart failure, angina pectoris, spasticity, glaucoma, diarrhea, and for the suppression of opiate withdrawal symptoms (J.P. Heible and R.R. Ruffolo Therapeutic Applications of Agents Interacting with α-Adrenoceptors, p. 180-206 in Progress in Basic and Clinical Pharmacology Vol. 8, P. Lomax and E.S. Vesell Ed., Karger, 1991). Adrenoceptor agonists such as clonidine have been primarily used orally, though a patch formulation is known. The goal of existing formulations is to deliver a systemic internal dose of the compound to the patient. The α_2 agonists are known to mediate vasoconstriction both in the core and periphery of a patient. In particular α_2 adrenoceptor agonists are known to cause vasoconstriction of peripheral arterioles, in response to stimulation due to cold or stress.

[0008] A number of patents describe the use of brimonidine for treating ophthalmic conditions and eye diseases. In Canadian patent No. CA2326690, there is described the use of topical ophthalmic preparations for use only in the eyes, to treat eye diseases. The Canadian patent discusses the problems with ophthalmic preparations taken topically (in the eye), orally or parenterally, and their systemic effects, including some serious, that limit their use. These systemic effects include, cardiopulmonary effects of β-blockers like timolol; dryness of mouth, flush, fever, tachy cardia, urinary retention, convulsion and irritability with atropine; hypertension with phenylephine; increased salivation, nausea, vomiting, diarrhea, stomach cramps, bronchial secretions, bronchial constriction, asthma, bradycardia, paresthesia with miotics; hypotension with clonidine; and dry mouth, fatigue and drowsiness with apraclonidine and brimonidine.

[0009] The research paper of Guarrera M. et al., "Flushing in Rosacea: A Possible Mechanism" Archives of Dermatological Research, vol. 272, No. 3/04, 1982, pages 311-316, discloses the oral administration of clonidine to inhibit flushing in patients affected by erythrogenic rosacea. The article of Rebora A., "The management if rosacea" American Journal of Clinical Dermatology, vol. 3, 2002, pages 489-496, describes the use of clonidine for the treatment of rosacea-associated flushing.

[0010] There has been no composition containing α_2 adrenoceptor agonists that can deliver a dose of the agonist to the patient, ameliorating the symptoms of rosacea, without causing systemic side effects. There has also been no topical skin composition containing α_2 adrenoceptor agonists that can deliver a dose of the agonist to the skin of the patient, ameliorating the symptoms of rosacea, without causing systemic side effects.

Summary Of The Invention

[0011] The present invention provides compositions and topical skin formulations for the treatment of rosacea-induced redness in accordance with claims 1 and 3. Compounds underlying the compositions of the invention are α_2 adrenoceptor agonists that act on the peripheral vasculature to cause vasoconstriction and thereby ameliorate the redness induced by rosacea. The compounds are delivered in a topical skin composition that ensures that the compounds are effective in the skin of a patient but do not penetrate the skin in sufficient amounts to induce serious systemic side effects.

[0012] Compounds underlying the compositions of the invention are : briminodine, oxymetazoline, xylometazoline, epinephrine, norepinephrine, phenylephrine, and methoxamine.

[0013] To treat rosacea-induced redness, the compositions of the invention are topically applied. The compounds are delivered in a topical formulation. Formulations for topical delivery of compounds are well-known in the art, such as aqueous or non-aqueous solutions or suspensions, creams, lotions, gels, or ointments.

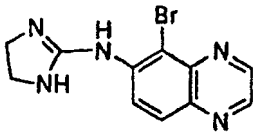
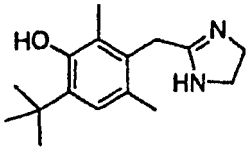
[0014] These and other features, aspects, and advantages of the invention will become better understood with reference to the following detailed description, examples, and appended claims.

Detailed Description

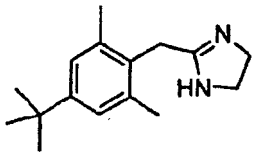
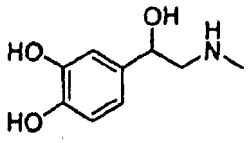
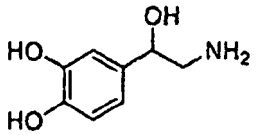
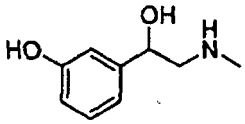
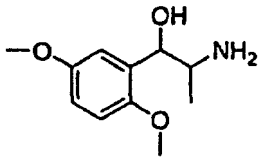
1.1 COMPOUNDS UNDERLYING THE COMPOSITIONS OF THE INVENTION

[0015] The α_2 adrenergic receptor agonist and/or a pharmaceutically acceptable salt thereof underlying the compositions of the present invention are selected from the group consisting of the compounds brimonidine, oxymetazoline, epinephrine, norepinephrine, phenylephrine, and methoxamine as listed in Table 1 below.

Table 1: Compounds Of The Invention

Compound of the Invention	Name
	(5-Bromo-quinoxalin-6-yl)-(4,5-dihydro-1H-imidazol-2-yl)-amine (Brimonidine)
	Oxymetazoline

(continued)

Compound of the Invention	Name
	Xylometazoline
	Epinephrine
	Norepinephrine
	Phenylephrine
	Methoxyamine

[0016] The most preferred compound is (5-Bromo-quinoxalin-6-yl)-(4,5-dihydro-1H-imidazol-2-yl)-amine (commonly referred to as brimonidine) and pharmaceutically acceptable salts thereof, particularly the tartrate salt.

[0017] The compounds described above are well known in the art to be α_2 adrenergic receptor agonists. As such, the compounds have powerful vasoconstricting effects when introduced into the body of mammals, particularly humans.

1.2 SYNTHESIS OF COMPOUNDS UNDERLYING THE COMPOSITIONS OF THE INVENTION

[0018] The compounds described above can be prepared in accordance with well-known synthetic procedures, for example, using the general synthetic procedures outlined in U.S. Patent Nos. 3,890,319 (issued June 17, 1975) and 4,029,792 (issued June 14, 1977).

1.3 TOPICAL FORMULATIONS OF THE INVENTION

[0019] The compounds described above are delivered to the affected area of the skin in a pharmaceutically acceptable topical carrier. As used herein, a pharmaceutically acceptable topical carrier is any pharmaceutically acceptable formulation that can be applied to the skin surface for topical, dermal, intradermal, or transdermal delivery of a pharmaceutical or medicament. The combination of a pharmaceutically acceptable topical carrier and a compound described above is termed a topical formulation of the invention. Topical formulations of the invention are prepared by mixing a compound described above with a topical carrier according to well-known methods in the art, for example, methods provided by standard reference texts such as, REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 1577-1591, 1672-1673, 866-885(Alfonso R Gennaro ed. 19th ed. 1995); Ghosh, T. K.; et al. TRANSDERMAL AND TOPICAL DRUG DELIVERY SYSTEMS (1997).

[0020] The topical carriers useful for topical delivery of compounds described above can be any carrier known in the art for topically administering pharmaceuticals, for example, but not limited to, pharmaceutically acceptable solvents,

such as a polyalcohol or water, emulsions (either oil-in-water or water-in-oil emulsions), such as creams or lotions; micro emulsions; gels; ointments; liposomes; powders; and aqueous solutions or suspensions, such as standard ophthalmic preparations.

1.3.1 Emulsions, Gels, and Ointments As Topical Carriers

[0021] In a preferred embodiment, the topical carrier used to deliver a compound described above is an emulsion, gel, or ointment. Emulsions, such as creams and lotions are suitable topical formulations for use in accordance with the invention. An emulsion is a dispersed system comprising at least two immiscible phases, one phase dispersed in the other as droplets ranging in diameter from 0.1 μm to 100 μm. An emulsifying agent is typically included to improve stability. When water is the dispersed phase and an oil is the dispersion medium, the emulsion is termed a water-in-oil emulsion. When an oil is dispersed as droplets throughout the aqueous phase as droplets, the emulsion is termed an oil-in-water emulsion. Emulsions, such as creams and lotions that can be used as topical carriers and their preparation are disclosed in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 282-291 (Alfonso R. Gennaro ed. 19th ed. 1995).

[0022] In another embodiment, the topical carrier used to deliver a compound described above is a gel, for example, a two-phase gel or a single-phase gel. Gels are semisolid systems consisting of suspensions of small inorganic particles or large organic molecules interpenetrated by a liquid. When the gel mass comprises a network of small discrete inorganic particles, it is classified as a two-phase gel. Single-phase gels consist of organic macromolecules distributed uniformly throughout a liquid such that no apparent boundaries exist between the dispersed macromolecules and the liquid. Suitable gels for use in the invention are disclosed in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 1517-1518 (Alfonso R. Gennaro ed. 19th ed. 1995). Other suitable gels for use in the invention are disclosed in U.S. Patent Nos. 6,387,383 (issued May 14, 2002); 6,517,847 (issued Feb. 11, 2003); and 6,468,989 (issued Oct. 22, 2002).

[0023] Polymer thickeners (gelling agents) that may be used include those known to one skilled in the art, such as hydrophilic and hydroalcoholic gelling agents frequently used in the cosmetic and pharmaceutical industries. Preferably, the hydrophilic or hydroalcoholic gelling agent comprises "CARBOPOL®" (B.F. Goodrich, Cleveland, Ohio), "HYPAN®" (Kingston Technologies, Dayton, N.J.), "NATROSOL®" (Aqualon, Wilmington, Del.), "KLUCEL®" (Aqualon, Wilmington, Del.), or "STABILEZE®" (ISP Technologies, Wayne, N.J.). Preferably the gelling agent comprises between about 0.2% to about 4% by weight of the composition. More particularly, the preferred compositional weight percent range for "CARBOPOL®" is between about 0.5% to about 2%, while the preferred weight percent range for "NATROLSOL®" and "KLUCEL®" is between about 0.5% to about 4%. The preferred compositional weight percent range for both "HYPAN®" and "STABILEZE®" is between 0.5% to about 4%.

[0024] "CARBOPOL®" is one of numerous cross-linked acrylic acid polymers that are given the general adopted name carbomer. These polymers dissolve in water and form a clear or slightly hazy gel upon neutralization with a caustic material such as sodium hydroxide, potassium hydroxide, triethanolamine, or other amine bases. "KLUCEL®" is a cellulose polymer that is dispersed in water and forms a uniform gel upon complete hydration. Other preferred gelling polymers include hydroxyethylcellulose, cellulose gum, MVE/MA decadiene crosspolymer, PVM/MA copolymer, or a combination thereof.

[0025] In another preferred embodiment, the topical carrier used to deliver a compound described above is an ointment. Ointments are oleaginous semisolids that contain little if any water. Preferably, the ointment is hydrocarbon based, such as a wax, petrolatum, or gelled mineral oil. Suitable ointments for use in the invention are well known in the art and are disclosed in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 1585-1591 (Alfonso R. Gennaro ed. 19th ed. 1995).

1.3.2 Aqueous Topical Formulations Of The Invention

[0026] In another embodiment, the topical carrier used in the topical formulations of the invention is an aqueous solution or suspension, preferably, an aqueous solution. Well-known ophthalmic solutions and suspensions are suitable topical carriers for use in the invention. Suitable aqueous topical formulations for use in the invention are disclosed in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 1563-1576 (Alfonso R. Gennaro ed. 19th ed. 1995). Other suitable aqueous topical carrier systems are disclosed in U.S. Patent Nos. 5,424,078 (issued Jun. 13, 1995); 5,736,165 (issued Apr. 7, 1998); 6,194,415 (issued Feb. 27, 2001); 6,248,741 (issued Jun. 19, 2001); 6,465,464 (issued Oct. 15, 2002).

[0027] The pH of the aqueous topical formulations of the invention are preferably within the range of from about 6 to about 8, more preferably, of from about 6.3 to about 6.5. To stabilize the pH, preferably, an effective amount of a buffer is included. In one embodiment, the buffering agent is present in the aqueous topical formulation in an amount of from about 0.05 to about 1 weight percent of the formulation. Acids or bases can be used to adjust the pH as needed. Suitable buffering agents are listed below in Section 1.3.3.

[0028] Tonicity-adjusting agents can be included in the aqueous topical formulations of the invention. Examples of suitable tonicity-adjusting agents include, but are not limited to, sodium chloride, potassium chloride, mannitol, dextrose, glycerin, and propylene glycol. The amount of the tonicity agent can vary widely depending on the formulation's desired properties. In one embodiment, the tonicity-adjusting agent is present in the aqueous topical formulation in an amount of from about 0.5 to about 0.9 weight percent of the formulation.

[0029] Preferably, the aqueous topical formulations of the invention have a viscosity in the range of from 0,015 to 0,025 Pa.s (about 15 cps to about 25 cps). The viscosity of aqueous solutions of the invention can be adjusted by adding viscosity adjusting agents, for example, but not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, or hydroxyethyl cellulose.

[0030] In a preferred embodiment, the aqueous topical formulation of the invention is isotonic saline comprising a preservative, such as benzalkonium chloride or chlorine dioxide, a viscosity-adjusting agent, such as polyvinyl alcohol, and a buffer system such as sodium citrate and citric acid.

1.3.3 Excipients

[0031] The topical formulations of the invention can comprise pharmaceutically acceptable excipients such as those listed in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 866-885 (Alfonso R. Gennaro ed. 19th ed. 1995; Ghosh, T. K.; et al. TRANSDERMAL AND TOPICAL DRUG DELIVERY SYSTEMS (1997), including, but not limited to, protectives, adsorbents, demulcents, emollients, preservatives, antioxidants, moisturizers, buffering agents, solubilizing agents, skin-penetration agents, and surfactants.

[0032] Suitable protectives and adsorbents include, but are not limited to, dusting powders, zinc sterate, collodion, dimethicone, silicones, zinc carbonate, aloe vera gel and other aloe products, vitamin E oil, allatoin, glycerin, petrolatum, and zinc oxide.

[0033] Suitable demulcents include, but are not limited to, benzoin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, and polyvinyl alcohol.

[0034] Suitable emollients include, but are not limited to, animal and vegetable fats and oils, myristyl alcohol, alum, and aluminum acetate.

[0035] Suitable preservatives include, but are not limited to, quaternary ammonium compounds, such as benzalkonium chloride, benzethonium chloride, cetrimide, dequalinium chloride, and cetylpyridinium chloride; mercurial agents, such as phenylmercuric nitrate, phenylmercuric acetate, and thimerosal; alcoholic agents, for example, chlorobutanol, phenylethyl alcohol, and benzyl alcohol; antibacterial esters, for example, esters of parahydroxybenzoic acid; and other antimicrobial agents such as chlorhexidine, chlorocresol, benzoic acid and polymyxin.

[0036] Chlorine dioxide (ClO_2), preferably, stabilized chlorine dioxide, is a preferred preservative for use with topical formulations of the invention. The term "stabilized chlorine dioxide" is well known in the industry and by those skilled in the art. Stabilized chlorine dioxide includes one or more chlorine dioxide precursors such as one or more chlorine dioxide-containing complexes and/or one or more chlorite-containing components and/or one or more other entities capable of decomposing or being decomposed in an aqueous medium to form chlorine dioxide. U.S. Patent No. 5,424,078 (issued Jun. 13, 1995), discloses a form of stabilized chlorine dioxide and a method for producing same, which can be used as a preservative for aqueous ophthalmic solutions and is useful in topical formulations of the invention. The manufacture or production of certain stabilized chlorine dioxide products is described in U.S. Pat. No. 3,278,447. A commercially available stabilized chlorine dioxide which can be utilized in the practice of the present invention is the proprietary stabilized chlorine dioxide of BioCide International, Inc. of Norman, OK, sold under the trademark Purogene™ or Purite™. Other suitable stabilized chlorine dioxide products include that sold under the trademark DuraKlor by Rio Linda Chemical Company, Inc., and that sold under the trademark Antheium Dioxide by International Dioxide, Inc.

[0037] Suitable antioxidants include, but are not limited to, ascorbic acid and its esters, sodium bisulfite, butylated hydroxytoluene, butylated hydroxyanisole, tocopherols, and chelating agents like EDTA and citric acid.

[0038] Suitable moisturizers include, but are not limited to, glycerin, sorbitol, polyethylene glycols, urea, and propylene glycol.

[0039] Suitable buffering agents for use in the invention include, but are not limited to, acetate buffers, citrate buffers, phosphate buffers, lactic acid buffers, and borate buffers.

[0040] Suitable solubilizing agents include, but are not limited to, quaternary ammonium chlorides, cyclodextrins, benzyl benzoate, lecithin, and polysorbates.

[0041] Suitable skin-penetration agents include, but are not limited to, ethyl alcohol, isopropyl alcohol, octylphenylpolyethylene glycol, oleic acid, polyethylene glycol 400, propylene glycol, N-decylmethylsulfoxide, fatty acid esters (e.g., isopropyl myristate, methyl laurate, glycerol monooleate, and propylene glycol monooleate); and N-methyl pyrrolidone.

1.3.4 Pharmaceutical Additives

[0042] The topical formulations of the invention can include pharmaceuticals or their pharmaceutically acceptable salts, for example, but not limited to, topical corticosteroids and other anti-inflammatory agents, such as betamethasone, diflorasone, amcinonide, fluocinolone, mometasone, hydrocortisone, prednisone, and triamcinolone; local anesthetics and analgesics, such as camphor, menthol, lidocaine, and dibucaine, and pramoxine; antifungals, such as ciclopirox, chloroxylenol, triacetin, sulconazole, nystatin, undecylenic acid, tolnaftate, miconizole, clotrimazole, oxiconazole, griseofulvin, econazole, ketoconozole, and amphotericin B; antibiotics and anti-infectives, such as mupirocin, erythromycin, clindamycin, gentamicin, polymyxin, bacitracin, and silver sulfadiazine; and antiseptics, such as iodine, povidine-iodine, benzalkonium chloride, benzoic acid, chlorhexidine, nitrofurazine, benzoyl peroxide, hydrogen peroxide, hexachlorophene, phenol, resorcinol, and cetylpyridinium chloride.

1.4 DOSAGE

[0043] Dosages and dosing frequency will be determined by a trained medical professional depending on the activity of the compound underlying the composition of the invention, the characteristics of the particular topical formulation, and the identity and severity of the dermatologic disorder treated.

[0044] In general, a compound described above is present in a formulation of the invention in an amount of from about 0.01 percent to about 5 percent of the total weight of the formulation, preferably, of from about 0.05 percent to about 1 percent, more preferably, of from about 0.1 1 percent to about 0.2 percent of the total weight of the formulation.

[0045] To treat rosacea-induced redness, the topical formulations of the invention are topically applied directly to the affected area in any conventional manner well known in the art. For example, by dropper or applicator stick, as a mist via an aerosol applicator, or by simply spreading a formulation of the invention onto the affected area with fingers. Generally the amount of a topical formulation of the invention applied to the affected skin area ranges from about 0.1 g/cm^2 of skin surface area to about 5 g/cm^2, preferably, 0.2 g/cm^2 to about 0.5 g/cm^2 of skin surface area. Typically, one to four applications per day are recommended during the term of treatment.

1.5 USE OF TOPICAL FORMULATIONS OF THE INVENTION IN COMBINATION WITH OTHER SKIN-DISORDER TREATMENT

[0046] The formulations of the invention can be used in combination with other treatments and medications to provide more effective treatment of rosacea-induced redness. The topical formulations of the invention can be used in combination with treatment regimens and medications well known for treatment of dermatologic disorders, such as those disclosed in THE MERCK MANUAL 811-830 (Keryn A.G. Lane et al. eds. 17th ed. 2001).

[0047] Using a formulation of the invention in combination with another medicament or treatment means administering a formulation of the invention and the other medicament or treatment to a subject in a sequence and within a time interval such that they can act together to treat rosacea-induced redness. For example, the compounds underlying the compositions of the invention can be administered at the same time as the other medicament in the same or separate formulations or at different times.

[0048] Any suitable route of administration can be employed to deliver the additional treatment or medication including, but not limited to, oral, intraoral, rectal, parenteral, topical, epicutaneous, transdermal, subcutaneous, intramuscular, intranasal, sublingual, buccal, intradural, intraocular, intrarespiratory, or nasal inhalation. Thus, the formulations of the invention can be administered together or at separate times with other medications or treatments.

[0049] In one embodiment, the topical formulations of the invention are used in combination with systemic administration of antibiotics or retinoids including, but not limited to, orally dosed antibiotics, such as tetracycline, minocin, minocycline, erythromycin, and doxycycline, and orally dosed retinoids such as isotretinoins (e.g., Accutane or Roaccutance).

[0050] In another embodiment, the topical formulations of the invention are used in combination with other topical treatments including, but not limited to, topical formulations consisting of metronidizole, hydrogen peroxide, benzoyl peroxide, lipoic acid, and azelaic acid, and sulfur preparations; topically dosed antibiotics, such as metronidazole, clindamycin, and erythromycin; topical retinoids such as tretinoin, adapalene, tazarotene; or topical steroids.

[0051] In another embodiment, the topical formulations of the invention are used in combination with mixed light pulse therapy (photoderm), pulsed dye laser treatment, or electrosurgery.

1.6 ARTICLE OF MANUFACTURE

[0052] Described herein is an article of manufacture that comprises a topical formulation of the invention in a suitable container with labeling and instructions for use. The container can be a dropper or tube with a suitable small orifice size, such as an extended tip tube made of any pharmaceutically suitable material.

[0053] The topical formulations of the invention can be filled and packaged into a plastic squeeze bottle or tube. Suitable container-closure systems for packaging topical formulations of the invention are commercially available, for example, from Wheaton Plastic Products, 1101 Wheaton Avenue, Millville, NJ 08332.

[0054] Preferably, instructions are packaged with the formulations of the invention, for example, a pamphlet or package label. The labeling instructions explain how to administer topical formulations of the invention, in an amount and for a period of time sufficient to treat rosacea-induced redness. The labeling instructions are an important aspect of the invention in that before a composition can be approved for any particular use, it must be approved for marketing by the United States Food and Drug Administration. Part of that process includes providing a label that will accompany the pharmaceutical composition that is ultimately sold. Preferably, the label includes the dosage and administration instructions, the topical formulation's composition, the clinical pharmacology, drug resistance, pharmacokinetics, absorption, bioavailability, and contraindications.

1.7 EXAMPLES

[0055] The following examples are provided for illustrative purposes only and are not to be construed as limiting the invention's scope in any manner.

1.7.1 Example 1: Synthesis of 5-Bromo-quinoxalin-6-yl)-(4,5-dihydro-1H-imidazol-2-yl)-amine

[0056] To a stirred solution of 6-amino-5-bromoquinoxaline hydrobromide (10 g) in distilled water (150 ml) is added thiophosgene (3 ml). The solution is stirred for two hours at room temperature and the resultant precipitate is collected by filtration, washed with water, and dried to afford 5-bromo-6-isothiocyanato-quinoxaline.

[0057] The 5-bromo-6-isothiocyanato-quinoxaline (3.5 g.) is directly dissolved in benzene (400 ml) and added dropwise to a well-stirred solution of ethylene diamine (15 g.) in benzene (50 ml). During a period of about two hours, an oil separates as a lower layer. The upper benzene layer is poured off and the oil is washed with diethyl ether and then dissolved in methanol (500 ml). The methanolic solution is refluxed until hydrogen sulfide evolution ceases. The methanolic solution is concentrated *in vacuo* to a volume of approximately 100 ml upon which a yellow solid precipitates. The precipitate is collected by filtration and recrystallized from methanol to afford of (5-Bromo-quinoxalin-6-yl)-(4,5-dihydro-1H-imidazol-2-yl)-amine: m.p. 250-251°C.

1.7.2 Example 2

[0058] An aqueous solution topical formulation of the invention comprises (5-Bromo-quinoxalin-6-yl)-(4,5-dihydro-1H-imidazol-2-yl)-amine-L-tartrate (brimonidine tartrate) (0.15 wt. %); Purite® (0.005%) (stabilized chlorine dioxide) as a preservative; and the inactive ingredients: boric acid; calcium chloride; magnesium chloride; potassium chloride; purified water; sodium borate; sodium carboxymethylcellulose; sodium chloride; with hydrochloric acid and/or sodium hydroxide to adjust the pH to 5.6 to 6.6. The osmolality is in the range of 250-350 mOsmol/kg.

1.7.3 Example 3

[0059] A aqueous solution topical formulation of the invention comprises (5-Bromo-quinoxalin-6-yl)-(4,5-dihydro-1H-imidazol-2-yl)-amine-L-tartrate, (brimonidine tartrate) (0.15 wt. %); benzalkonium chloride (0.005 wt. %) as a preservative; and the inactive ingredients: boric acid; calcium chloride; magnesium chloride; potassium chloride; purified water; sodium borate; sodium carboxymethylcellulose; sodium chloride; with hydrochloric acid and/or sodium hydroxide to adjust the pH to 5.6 to 6.6. The osmolality is in the range of 250-350 mOsmol/kg.

1.7.4 Example 4

[0060] A possible cream topical formulation of the invention is described in the Table below.

Possible Cream Formulation Of The Invention (Hydrophilic Ointment USP)

Ingredient	Weight Percent
Brimonidine tartrate	0.15%
Stearic acid	7%
Stearyl alcohol	5%

(continued)

Ingredient	Weight Percent
Cetyl alcohol	2%
Glycerin	10%
Sodium lauryl sulfate	1%
Propylparaben	0.05%
Methylparaben	0.25%
Disodium edetate	0.055
Distilled water	QS

[0061] Melt the stearyl alcohol and the white petrolatum on a steam bath, and warm to about 75 degrees C. Add the other ingredients, previously dissolved in the water and warmed to 75 degrees C, and stir the mixture until it congeals. With stirring, allow the mixture to cool and add brimonidine tartrate as a concentrated solution.

1.7.5 Example 5

[0062] A possible ointment topical formulation of the invention is described in the Table below.

Possible Ointment Formulation of the Invention (Hydrophilic Ointment USP)

Ingredients	Weight
Brimonidine tartrate	10g
Cholesterol	30g
Stearyl Alcohol	30g
White Wax	80g
White Petrolatum	850g

[0063] Mix the stearyl alcohol and white wax together on a steam bath, then add the cholesterol and stir until it completely dissolves. Add the white petrolatum and mix. Remove from the bath, and stir until the mixture congeals. Continue stirring and add brimonidine tartrate as a concentrated slurry.

1.7.6 Example 6

[0064] A possible gel formulation of the invention is described in the table below.

Possible Gel Formulation of the Invention

Ingredients	Weight %
Brimonidine tartrate	1.0%
Methylparaben NF	0.15%
Propylparaben NF	0.03%
Hydroxyethylcellulose NF	1.25%
Disodium Edetate USP	0.05%
Purified Water, USP	QS 100%

1.7.7 Example 7

[0065] A possible gel formulation of the invention is described in the Table below.

Possible Gel Formulation of the Invention

Ingredients	Weight %
Brimonidine tartrate	1.0%
Methylparaben	0.20%
Propylparaben	0.05%
Carbomer 934P NF	1.0%
Sodium Hydroxide	QS pH 7
Purified Water USP	QS 100%

[0066] The ingredients are mixed together and aqueous sodium hydroxide is slowly added to the mixture until a pH of about 7 is reached and the gel is formed.

1.7.8 Example 8

[0067] A possible gel formulation of the invention is described in the Table below.

Possible Gel Formulation of the invention

Ingredients	Weight %
Brimonidine tartrate	1.0%
Methylparaben	0.2%
Propylparaben	0.05%
"CARBOPOL®"	1.0%
Triethanolamine	QS pH 7
Water	QS 100 %

[0068] The ingredients are mixed together and stirred. Triethanolamine is added until a pH of about 7 is attained.

1.7.9 Example 9

[0069] Alphagan P (0.15% brimonidine tartrate in isotonic saline and citrate buffer having a pH of 6.3 to 6.5) was supplied by Allergan, Inc. having the composition disclosed in Example 2 above. A study was conducted with four otherwise healthy persons who were independently diagnosed with phase II rosacea (characterized by transitory erythema of the mid-facial areas and early telangiectasis). All subjects followed a morning protocol of cleansing their face with soap and water. After a gentle towel drying and air drying, Alphagan-P was administered by gently rubbing onto areas of facial redness. The application area was again allowed to air dry without any dressing.

[0070] Subject 1 is a 59 year old woman with a ten year history of rosacea displaying symptoms of periodic redness flare-ups across her cheeks that usually runs a course of three to four weeks before subsiding under customary dermatological treatment. The subject showed an immediate improvement after the first morning application of Alphagan-P. All redness disappeared within 10 minutes and her face remained symptom free for the entire first day. Daily observation showed only mild return of redness after 24 hours. Continued daily use resulted in completely eliminating the redness due to rosacea in three days.

[0071] Subject 2 is a 54 year-old woman with an eight year history of rosacea who suffers from everyday facial redness across her cheeks with occasional severe flare-ups. The subject halted her customary daily dermatological treatment to try the protocol described above. The result was the same immediate removal of all redness within ten minutes. The dramatic improvement lasted most of the day with some mild redness re-occurring in the evening. For this subj ect, redness returned the next day. Continued daily use provided daily relief from redness.

[0072] Subject 3 is a 57 year-old man with a greater than ten-year history of rosacea displaying symptoms of redness of the cheeks and the nose. Although this subject's redness due to rosacea is always present, his general ruddy complexion and lack of concern allows him to forgo the daily use of customary dermatological treatment in favor of occasional,

ad hoc treatments. A single morning trial of the Alphagan-P protocol described above resulted in dramatic daylong relief of redness.

[0073] Subject 4 is a woman in her early forties with a diagnosis of rosacea on her lower face and chin. Her condition includes some thickening of skin. Upon trying the protocol, redness was greatly reduced but not completely eliminated. Qualitatively the reduction was described as 80% less red. An additional observation of reduced skin thickening was reported.

These trials demonstrate that 0.15% brimonidine tartrate, when used in a daily morning protocol, dramatically eliminates or reduces redness due to rosacea. It is shown to be an effective treatment to greatly accelerate the arrest of a rosacea flare-up. It is further shown to be an effective daily treatment for chronic rosacea redness.

1.7.10 Example 10

Use of oxymetazoline

[0074] An oxymetazoline solution (Afrin®, 0.05% solution. Schering-Plough HealthCare Products) The solution was placed onto a cotton tipped swab and applied to approximately 4 cm^2 of naso-facial skin displaying rosacea induced erythema. Twenty two minutes after application a lessening of erythema was observed.

1.7.11 Example 11

Use of epinephrine

[0075] An epinephrine solution (Epipen®, trademark of Dey®, L.P.) containing approximately 0.3 mg of epinephrine was placed in a glass container. The solution was placed onto a cotton tipped swab and then applied to approximately 4 cm^2 of naso-facial skin displaying rosacea induced erythema. Within 5 minutes of application a mottled whitening of the skin was observed. No whitening was observed in skin outside of the application area. The whitening effect began to fade after approximately 30 minutes.

1.7.12 Example 12 (Comparative Example)

[0076] A tetrahydrozoline solution (Visine®, 0.05% solution, Pfizer) The solution was placed onto a cotton-tipped swab and applied to approximately 4 cm^2 of naso-facial skin displaying rosacea induced erythema. Visual observation indicated no erythema reduction using this concentration of tetrahydrozoline.

1.7.13

Testing Procedure For Prevention of Redness By α-Adrenergic Agonists:

[0077] A number of α-adrenergic agonists were evaluated for their ability to topically suppress erythema in human skin induced by methyl nicotinate. The erythema produced in the skin results from the vasodilatory effect on the dermal vasculature by methyl nicotinate. In this model, the minimum erythemal dose (MED) produced on the forearm by methyl nicotinate is determined for each test subject. The MED is defined as the minimal dose that results in a defined circle of erythema. The MED was determined by saturating five 19 mm Hill Top Chambers with 220 μl of 1, 2, 3, 4, and 5 mm methyl nicotinate. The Hill Top Chambers were applied to the volar forearm of each test subject, removed after 30 seconds and excess liquid lightly blotted from the skin. The MED of methyl nicotinate was selected 10 minutes after application, by determining the minimal dose that resulted in a defined circle of erythema. The α-adrenergic agonists were dissolved in alcohol and topically applied ($2\mu l/cm^2$) to selected sites on the contralateral volar forearm for 30 minutes prior to challenge with methyl nicotinate. Hill Top Chambers (19 mm) were saturated with 220 μl of the dose of methyl nicotinate determined to produce a MED for each test subject. The chambers were applied to the volar forearm treated with vehicle or test compounds, removed after 30 seconds and excess liquid was lightly blotted from the skin. Ten minutes after application of methyl nicotinate the test sites were evaluated for erythema. A numerical grading scale of 0 to 3 was used: 0=none, 0.5=barely perceptible, 1.0=mild, 1.5=mild+ (mild to moderate), 2.0=moderate, 2.5=moderate+ (moderate to severe), 3.0=severe.

[0078] The test results are shown in the table below and indicate that each of the tested compounds reduced the formation of the Methyl Nicotinate induced redness (erythema) in the test subjects. With both Oxymetazoline HCl and Naphazoline HCl the redness was fully blocked for two of the three subjects pursuant to the test conditions as described above.

The Effect of α-Adrenergic Agonists on Methyl Nicotinate-Induced Erythema

Pre-Treatment + Methyl Nicotinate	N	Mean Erythema Grade
Alcohol Vehicle Control	3	3.0
0.2% Naphazoline HCl*	3	0.33
0.2% Oxymetazoline HCl	3	1.0
0.2% Brimonidine	3	0.83

*Not within scope of appended claims

1.8 DEFINITIONS

[0079] The phrase "pharmaceutically acceptable salt(s)", as used herein, means those salts of compounds of the invention that are safe and effective for topical use in mammals and that possess the desired biological activity. Pharmaceutically acceptable salts include salts of acidic or basic groups present in compounds of the invention. Pharmaceutically acceptable acid addition salts include, but are not limited to, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzensulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Certain compounds underlying the compositions of the invention can form pharmaceutically acceptable salts with various amino acids. Suitable base salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, and diethanolamine salts. For a review on pharmaceutically acceptable salts see BERGE ET AL., 66 J. PHARM. SCI. 1-19 (1977).

[0080] The term "pharmaceutically acceptable topical formulation" as used herein means any formulation which is pharmaceutically acceptable for topical delivery of the compounds underlying the compositions of the invention. According to the invention, a "topical formulation" will comprise at least a compound underlying the compositions of the invention. The choice of topical formulation will depend on several factors, including the nature of the symptoms to be treated, the physiochemical characteristics of the particular compound underlying the compositions of the invention and of other excipients present, their stability in the formulation, available manufacturing equipment, and cost constraints.

[0081] As used herein, a "therapeutically effective amount of a compound underlying the compositions of the invention" means the minimum amount of the compound that is effective to treat rosacea-induced redness.

[0082] As used herein, the term "subject" means any animal, preferably a mammal, to which will be or has been administered topical formulations of the invention. The term "mammal" as used herein, encompasses any mammal. Examples of mammals include, but are not limited to, cows, horses, sheep, pigs, cats, dogs, mice, rats, rabbits, guinea pigs, monkeys, humans etc., more preferably, a human. Preferably, a subject is in need of treatment or prevention of rosacea-induced redness.

[0083] In one embodiment, "treatment" or "treating" refers to an amelioration, or reversal of a rosacea-induced redness. For example, treating rosacea-induced redness by lessening the redness of the skin.

[0084] As used herein, "carbomer" is the USP designation for various polymeric acids that are dispersible but insoluble in water. When the acid dispersion is neutralized with a base a clear, stable gel is formed. Carbomer 934P is physiologically inert and is not a primary irritant or sensitizer. Other carbomers include 910, 940, 941, and 1342.

[0085] One of ordinary skill in the art can make many variations and modifications to the above-described embodiments of the invention without departing from the scope of the appended claims.

Claims

1. Use of a composition comprising:

at least one of an α_2 adrenergic receptor agonist and a pharmaceutically acceptable salt thereof; and
a pharmaceutically acceptable carrier
for the preparation of a medicament for treating rosacea-induced redness, wherein said composition is to be topically applied directly to the affected area of skin of a patient in need of such treatment to decrease blood flow through the small arteries or arterioles of the skin of the patient, and wherein said composition acts locally in the skin of the patient,
wherein the at least one of an α_2 adrenergic receptor agonist and a pharmaceutically acceptable salt thereof

is selected from the group consisting of brimonidine, oxymetazoline, xylometazoline, epinephrine, norepinephrine, phenylephrine, and methoxamine.

2. A use according to claim 1, wherein the pharmaceutically acceptable carrier is selected from the group consisting of sprays, mists, aerosols, solutions, lotions, gels, creams, ointments, pastes, unguents, emulsions, and suspensions.

3. A topical composition for use in a method of treating rosacea-induced redness, said topical composition comprising:

at least one of an α_2 adrenergic receptor agonist and a pharmaceutically acceptable salt thereof;
and a pharmaceutically acceptable carrier,
wherein said composition is to be topically applied directly to the affected area of skin of a patient in need of such treatment to decrease blood flow through the small arteries or arterioles of the skin of the patient, and wherein said composition acts locally in the skin of the patient,
wherein the at least one of an α_2 adrenergic receptor agonist and a pharmaceutically acceptable salt thereof is selected from the group consisting of brimonidine, oxymetazoline, xylometazoline, epinephrine, norepinephrine, phenylephrine, and methoxamine.

4. The topical composition for use according to claim 3, wherein the pharmaceutically acceptable carrier is selected from the group consisting of sprays, mists, aerosols, solutions, lotions, gels, creams, ointments, pastes, unguents, emulsions, and suspensions.

5. The topical composition for use according to claim 3, wherein the at least one of an α_2 adrenergic receptor agonist and a pharmaceutically acceptable salt thereof is present in an amount in the range of about 0.01 to 5 weight percent.

6. The topical composition for use according to claim 3, wherein the pH value of the composition is in the range of about 5 to 8.

7. The topical composition for use according to claim 3, further comprising a preservative.

8. The topical composition for use according to claim 3, further comprising a local anesthetic.

9. The topical composition for use according to claim 3, further comprising a skin humectant.

10. A use according to claim 1, or a topical composition for use according to claim 3, wherein the at least one of an α_2 adrenergic receptor agonist and a pharmaceutically acceptable salt thereof is brimonidine.

Patentansprüche

1. Verwendung einer Zusammensetzung, umfassend:

zumindest eines von einem α_2 adrenergen Rezeptoragonisten und einem pharmazeutisch geeigneten Salz davon; und
einen pharmazeutisch geeigneten Träger
für die Herstellung eines Medikaments zur Behandlung von Rosacea-induzierter Rötung, wobei die Zusammensetzung topisch direkt auf der betroffenen Fläche der Haut eines Patienten, der einer solchen Behandlung bedarf, anzuwenden ist, um den Blutfluss durch die kleinen Arterien oder Arteriolen der Haut des Patienten zu senken, und wobei die Zusammensetzung lokal auf der Haut des Patienten wirkt, wobei der zumindest eine von einem α_2 adrenergen Rezeptoragonisten und einem pharmazeutisch geeigneten Salz davon ausgewählt ist aus der Gruppe bestehend aus Brimonidin, Oxymetazolin, Xylometazolin, Adrenalin, Noradrenalin, Phenylephrin, und Methoxamin.

2. Verwendung nach Anspruch 1, wobei der pharmazeutisch geeignete Träger ausgewählt ist aus der Gruppe bestehend aus Sprays, Nebeln, Aerosolen, Lösungen, Lotionen, Gelen, Cremes, Salben, Pasten, Unguenten, Emulsionen, und Suspensionen.

3. Topische Zusammensetzung zur Verwendung in einem Verfahren zur Behandlung von Rosacea-induzierter Rötung, wobei die topische Zusammensetzung umfasst:

zumindest einen von einem α_2 adrenergen Rezeptoragonisten und einem pharmazeutisch geeigneten Salz davon;
und einen pharmazeutisch geeigneten Träger,
wobei die Zusammensetzung topisch direkt auf der betroffenen Fläche der Haut eines Patienten, der einer solchen Behandlung bedarf, anzuwenden ist, um den Blutfluss durch die kleinen Arterien oder Arteriolen der Haut des Patienten zu senken, und wobei die Zusammensetzung lokal auf der Haut des Patienten wirkt,
wobei der zumindest eine von einem α_2 adrenergen Rezeptoragonisten und einem pharmazeutisch geeigneten Salz davon ausgewählt ist aus der Gruppe bestehend aus Brimonidin, Oxymetazolin, Xylometazolin, Adrenalin, Noradrenalin, Phenylephrin, und Methoxamin.

4. Die topische Zusammensetzung zur Verwendung nach Anspruch 3, wobei der pharmazeutisch geeignete Träger ausgewählt ist aus der Gruppe bestehend aus Sprays, Nebeln, Aerosolen, Lösungen, Lotionen, Gelen, Cremes, Salben, Pasten, Unguenten, Emulsionen, und Suspensionen.

5. Die topische Zusammensetzung zur Verwendung nach Anspruch 3, wobei der zumindest eine α_2 adrenerge Rezeptoragonist und ein pharmazeutisch geeignetes Salz davon in einer Menge im Bereich von 0,01 bis 5 Gewichtsprozent vorhanden ist.

6. Die topische Zusammensetzung nach Anspruch 3, wobei der pH Wert der Zusammensetzung im Bereich von etwa 5 bis 8 liegt.

7. Die topische Zusammensetzung zur Verwendung nach Anspruch 3, die ferner einen Konservierungsstoff umfasst.

8. Die topische Zusammensetzung zur Verwendung nach Anspruch 3, die ferner ein Lokalanästhetikum umfasst.

9. Die topische Zusammensetzung zur Verwendung nach Anspruch 3, die ferner ein Hautbefeuchtungsmittel umfasst.

10. Verwendung nach Anspruch 1, oder eine topische Zusammensetzung zur Verwendung nach Anspruch 3, wobei der zumindest eine von einem α_2 adrenergen Rezeptoragonisten und einem pharmazeutisch geeigneten Salz davon Brimonidin ist.

Revendications

1. Utilisation d'une composition comprenant :

au moins l'un d'un agoniste de récepteur adrénergique α_2 et d'un sel pharmaceutiquement acceptable de celui-ci ; et
un vecteur pharmaceutiquement acceptable,
pour la préparation d'un médicament destiné au traitement d'une rougeur induite par une rosacée, où ladite composition est destinée à être appliquée par voie topique directement à la zone affectée de la peau d'un patient ayant besoin d'un tel traitement pour réduire le flux sanguin à travers les petites artères ou les artérioles de la peau du patient, et où ladite composition agit localement dans la peau du patient,
où l'au moins un d'un agoniste de récepteur adrénergique α_2 et d'un sel pharmaceutiquement acceptable de celui-ci est choisi dans le groupe consistant en la brimonidine, l'oxymétazoline, la xylométazoline, l'épinéphrine, la norépinéphrine, la phényléphrine et la méthoxamine.

2. Utilisation selon la revendication 1, où le vecteur pharmaceutiquement acceptable est choisi dans le groupe consistant en les sprays, les brumisations, les aérosols, les solutions, les lotions, les gels, les crèmes, les pommades, les pâtes, les onguents, les émulsions et les suspensions.

3. Composition topique destinée à être utilisée dans un procédé de traitement d'une rougeur induite par une rosacée, ladite composition topique comprenant :

au moins l'un d'un agoniste de récepteur adrénergique α_2 et d'un sel pharmaceutiquement acceptable de celui-ci ;
et un vecteur pharmaceutiquement acceptable,
où ladite composition est destinée à être appliquée par voie topique directement à la zone affectée de la peau

d'un patient ayant besoin d'un tel traitement pour réduire le flux sanguin à travers les petites artères ou les artérioles de la peau du patient, et où ladite composition agit localement dans la peau du patient,
où l'au moins un d'un agoniste de récepteur adrénergique α_2 et d'un sel pharmaceutiquement acceptable de celui-ci est choisi dans le groupe consistant en la brimonidine, l'oxymétazoline, la xylométazoline, l'épinéphrine, la norépinéphrine, la phényléphrine et la méthoxamine.

4. Composition topique selon la revendication 3, où le vecteur pharmaceutiquement acceptable est choisi dans le groupe consistant en les sprays, les brumisations, les aérosols, les solutions, les lotions, les gels, les crèmes, les pommades, les pâtes, les onguents, les émulsions et les suspensions.

5. Composition topique destinée à être utilisée selon la revendication 3 où l'au moins un d'un agoniste de récepteur adrénergique α_2 et d'un sel pharmaceutiquement acceptable de celui-ci est présent en une quantité dans la plage d'environ 0,01 à 5 % en poids.

6. Composition topique destinée à être utilisée selon la revendication 3 où le pH de la composition est dans la plage d'environ 5 à 8.

7. Composition topique destinée à être utilisée selon la revendication 3 comprenant en outre un conservateur.

8. Composition topique destinée à être utilisée selon la revendication 3 comprenant en outre un anesthésique local.

9. Composition topique destinée à être utilisée selon la revendication 3 comprenant en outre un humectant cutané.

10. Utilisation selon la revendication 1 ou composition topique destinée à être utilisée selon la revendication 3 où l'au moins un d'un agoniste de récepteur adrénergique α_2 et d'un sel pharmaceutiquement acceptable de celui-ci est la brimonidine.

REFERENCES CITED IN THE DESCRIPTION

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